REMARKS

Upon entry of the amendments, claims 2, 3, 8-13, 19-21, 34, 39, and 41-50 constitute the pending claims in the present application. Claims 4-7 have been cancelled. Applicants reserve the right to pursue the cancelled subject matter in this or other applications. Claims 46-50 are withdrawn as being directed to a non-elected species or invention. Applicants respectfully request rejoinder of the withdrawn species claims upon allowance of a linking claim.

Claim 34 has been amended to recite "disorder caused by a deficiency of Purkinje neurons." Support for this amendment may be found, for example, in paragraphs 104 and 105 of the published application, US 2004-0115175. Claims 19-21 have been amended to correct antecedent basis.

Applicants concurrently submit an Information Disclosure Statement, and respectfully request consideration of the publications therein.

Applicants respectfully request reconsideration in view of the following remarks. Issues raised by the Examiner will be addressed below in the order they appear in the prior Office Action.

1. Claim rejections under 35 U.S.C. §112, first paragraph, written description

Claims 2, 3, 8-13, 19-21, 34, 39, and 41-45 are rejected under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. Applicants respectfully traverse this rejection to the extent it is maintained over the claims as amended.

The Examiner argues that "[t]he original disclosure fails to teach an agent that mobilized bone marrow cells also 'induces' formation of the Purkinje/bone marrow-derived heterokaryon in the nervous system of the individual as now claimed" (page 5 of the recent Office Action). To the contrary, the pending claims are fully enabled, and do not constitute new matter.

The specification as originally filed teaches:

"Also provided are methods for treating a neuron deficiency by **administering a bone marrow cell mobilization therapy to an individual having a neuron**

> **deficiency, thereby inducing formation of bone marrow derived neurons in the nervous system of the subject;** and ameliorating at least one symptom of the neuron deficiency." (paragraph 15 of the published application; emphasis added)

The specification goes on to describe the "bone marrow derived neurons" of the above-quoted sentence, in paragraph 10 of the published application:

> "While, in certain embodiments, the precise mechanism by which bone marrow derived neurons form is of secondary importance to the eventual clinical effect, examples of such mechanisms include **fusion between a bone marrow derived cell and a neuron (particularly a Purkinje cell) to generate a heterokaryon...**" (emphasis added)

Therefore, the specification as-filed teaches that bone marrow transplants and bone marrow cell mobilization therapies are two ways of increasing the number of bone marrow cells in the bloodstream, which in turn promotes the formation of heterokaryons between bone marrow derived cells and Purkinje neurons. Clearly, the specification, as originally filed, describes the use of bone cell mobilization agents (such as G-CSF) to generate a heterokaryon formed from a bone marrow cell and a Purkinje cell. Thus, the amendments do not introduce new matter.

Applicants submit that one of skill in the art at the time of filing would have recognized that Applicants were in possession of the invention as currently claimed, and that the present claims are adequately supported by the specification as-filed. Reconsideration and withdrawal of the written description rejection is respectfully requested.

2. Claim rejections under 35 U.S.C. §112, first paragraph, enablement

Claims 2, 3, 8-13, 19-21, 34, 39, and 41-45 are rejected under 35 U.S.C. §112, first paragraph, as allegedly failing to comply with the enablement requirement. Applicants respectfully traverse this rejection to the extent it is maintained over the claims as amended.

The Office Action argues that "the intended use of the method is for therapy of a neuron deficiency, and hence instant claims still embrace a therapeutic method drawn to treating a neuronal

deficiency by administering a bone marrow cell mobilization therapy, and will be evaluated by th[is] standard" (page 8). Applicants respectfully traverse.

2.1 Limitations from the specification may not be imported into the claims

Applicants submit that the Examiner has improperly applied the standard of enablement to a claim not before the Examiner. Specifically, the enablement rejection alleges that the application does not teach *how to use* the claims for a "therapeutic use." However, this is not what is being claimed. Claim 34 as amended does not recite "therapeutic use" or any language requiring amelioration of neurological symptoms. Rather, therapeutic use is merely one of many possible uses of the presently claimed method described in the specification (see point 2.2 below). The Examiner is essentially importing a limitation *described in the specification, but not presently claimed,* into the pending claims, and applying the enablement standard to the resulting claim. This is improper: "[l]imitations appearing in the specification but not recited in the claim are not read into the claim. *E-Pass Techs., Inc. v. 3Com Corp.*, 343 F.3d 1364, 1369, 67 USPQ2d 1947, 1950 (Fed. Cir. 2003)" (MPEP 2106).

The sole inquiry in examining Claim 34 for enablement should be: whether one of skill in the art can **make** (*i.e.*, practice) and **use** (*i.e.*, perform at least *one* use, see point 2.2 below) the claimed invention without undue experimentation. If one of skill in the art can administer said agent to said individual to induce the formation of said heterokaryon (which the Examiner does not dispute), and if one of skill in the art can use this method in at least one use (such as research use), then Claim 34 is enabled to its full scope.

Thus, the Examiner's interpretation of the claim is improper, and the enablement rejection is in error.

2.2 Only one use need be enabled

The Office Action states on page 8, "the intended use of the method is for therapy of a neuron deficiency." The Examiner then argues that this use is not enabled, and thus claim 34 is not enabled. (The "intended use of instantly claimed invention still is therapeutic, and thus proper to be evaluated by the standard," page 14 of the Office Action.) In other words, the Examiner does not

dispute that the claims are enabled in terms of "how to make," but the Examiner argues that the claimed methods are not enabled in terms of "how to use."

To meet the "how-to-use" aspect of the enablement requirement under 35 U.S.C. § 112, first paragraph, Applicants need only provide one use for the claimed methods. Pursuant to MPEP 2164.01(b), "[a]s long as the specification discloses at least one method for making and using the claimed invention that bears a reasonable correlation to the entire scope of the claim, then the enablement requirement of 35 U.S.C. 112 is satisfied. *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970)." The claimed methods may be used for many purposes, of which therapeutic use is only one. For example, the claimed methods may also be used in research to study the mechanism of heterokaryon formation. This is clear from the specification, where the working examples show the formation *in mice, in an experimental setting,* of bone marrow-derived cell/Purkinje neuron heterokaryons. For example, paragraph 123 states that certain experiments were performed to "elucidate the mechanism by which BMDCs contribute to neural tissue." Applicants have at least enabled the *experimental* use of the claimed methods. Hence, the "how-to-use" aspect of the enablement requirement under 35 U.S.C. § 112, first paragraph is met.

2.3 The claims are not directed to therapeutic uses per se

Claim 34 claims a method of "producing a Purkinje/bone marrow-derived heterokaryon". Production of a heterokaryon is not a therapeutic use *per se*. Not every method that can conceivably have a therapeutic use is in fact a therapeutic method claim. The Federal Circuit has clearly shown the distinction between a therapeutic use and other uses. For example, the Federal Circuit has previously held, in Cross v. Iizuka, 753 F.2d 1040, 224 USPQ 739 (Fed. Cir. 1985), that claims to imidazole derivatives are valid because they enabled a pharmacological activity, though not a therapeutic use. The Federal Circuit agreed with the Board, which "... held that tests evidencing pharmacological activity may manifest a practical utility even though they may not establish a specific therapeutic use." Thus, whether the instant specification enables a therapeutic use of G-CSF is irrelevant, because the claims do not recite any therapeutic use.

2.4 Working examples are not necessary to meet the enablement standard

To support the enablement argument, the Examiner states that the "specification fails to

provide any evidence that administering G-CSF, or any agent [for] that matter, would induce the formation of new Purkinje neuron[s]" (page 9). However, according to MPEP 2164.02, the "specification need not contain an example if the invention is otherwise disclosed in such manner that one skilled in the art will be able to practice it without an undue amount of experimentation." Applicants have made the unequivocated statement that one may administer G-CSF to form BMDC-Purkinje heterokaryons. Even in the absence of a working example, a "specification disclosure which contains a teaching of the manner and process of making and using an invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as being in compliance with the enablement requirement of 35 U.S.C. 112, first paragraph, *unless there is a reason to doubt the objective truth of the statements contained therein* which must be relied on for enabling support." (MPEP 4164.04; emphasis added). Thus, if the Examiner doubts that G-CSF administration can cause formation of BDMC/Purkinje heterokaryons, the burden is on the Examiner to provide evidence for this position. So far, the Examiner has not carried this burden.

Even in the absence of actual working examples, Applicants have provided sufficient data to show that the administration of bone marrow mobilization agents is (at least) likely to produce BMDC/Purkinje neuron heterokaryons. G-CSF is a recognized bone marrow cell mobilization agent. Thus, it seems reasonable to conclude that G-CSF treatment causes the mobilization of more than one bone marrow cell in a subject. Applicants remind the Examiner of the Rule 132 Declaration submitted October 31, 2007, in which Applicants showed that administration of only one bone marrow cell was sufficient to form a BMDC/Purkinje heterokaryon. Thus, the specification provides evidence that one skilled in the art can readily produce BMDC/Purkinje heterokaryons by administration of a bone marrow cell mobilization agent.

2.5 Bone marrow mobilization therapies may substitute for injection of bone marrow cells

On page 14 of the Office Action, the Examiner takes issue with Applicants' statement, on page 9 the prior Response, that "administering an agent that mobilizes bone marrow cells can serve as a substitute for injection of bone marrow cells." It is clear from the context of Applicants' sentence that Applicants meant that bone marrow mobilization agents may substitute for injection of

bone marrow cells *for the purpose of increasing the number of mobilized bone marrow-derived cells in the blood stream.* Specifically, the preceding sentence on page 9 of the Response in question states, "it was well-known in the art that bone marrow cell mobilization therapy (or administration of an agent that mobilizes bone marrow cells) results in the movement of bone marrow cells into the circulation." The Examiner argues that bone marrow mobilization agents are not acceptable substitutes for bone marrow injections *for other purposes, such as restoring the bone marrow of a patient whose bone marrow was destroyed by ablative therapy.* However, this argument appears to have missed the point, since Applicants' argument was that both bone marrow mobilization agents and injection of bone marrow cells are acceptable methods *for increasing the number of mobilized bone marrow cells in the bloodstream* in a patient that has bone marrow cells. The Examiner has not rebutted this argument. In fact, she has acknowledged this reasoning on page 20 of the Office Action: "bone marrow cell mobilization therapies were widely practiced in the art at the time of the instant priority date, and it was widely known that such therapies result in the movement of bone marrow cells from the bone marrow into the circulation." Accordingly, Applicants request withdrawal of this ground of rejection under the enablement requirement.

2.6 Legal standards of Enablement and Written Description are Distinct

Applicants also note that on page 7 of the recent Office Action, the Examiner alleges that the claims lack written description, and therefore lack enablement as well. This statement is legally incorrect. Pursuant to MPEP 2161, "[t]he written description requirement is separate and distinct from the enablement requirement." A finding of lack of written description does not automatically lead to a conclusion of lack of enablement, and vice versa. Thus, without more, the Examiner's arguments regarding written description are insufficient to make a *prima facie* case for lack of enablement.

For the reasons presented above, Applicants submit that, at the art at the time of filing, the specification fully enabled one of ordinary skill to make and use the claimed invention, and that the present claims are adequately supported by the specification. Reconsideration and withdrawal of this rejection is respectfully requested.

3. Obvious misstatement in the previous Response

Applicants wish to bring the Examiner's attention to an obvious misstatement in an argument made in the previous Response. As background information, since the date of filing, Applicants have argued that both bone marrow mobilization agents and injection of bone marrow cells are acceptable methods for increasing the number of mobilized bone marrow cells in the bloodstream. However, in the previous Response, Applicants inadvertently stated the contrary in a sentence with a triple negative. In the previous response, Applicants stated that "[s]ince Applicants have already demonstrated that injected bone marrow cells can navigate the blood circulation and find their way to the CNS... there is no scientific reason to doubt that mobilized bone marrow cells *cannot* do the same," (emphasis added, see page 9 of the previous response). Obviously, Applicants meant to say "*can*" instead of "*cannot*" in that sentence. However, judging from the Examiner's most recent Office Action, the Examiner understood the substance of Applicants' arguments and was not misled by this misstatement.

4. Claim rejections under 35 U.S.C. §102

4.1 Claims rejections under 35 U.S.C. § 102 in view of Rudolph *et al.*

Claims 2, 3, 21, 34, 39, and 41-45 are rejected under 35 U.S.C. §102(b) as allegedly being anticipated by Rudolph *et al.* (J Neural Transm 1997; 104:1305-1311). Specifically, the Examiner alleges that G-CSF was administered to a patient suffering from Parkinson's disease. Applicants respectfully traverse the rejection to the extent it is applicable to the claims as amended.

Claim 34, as amended, refers to a patient with a "disorder caused by a deficiency of Purkinje neurons." Parkinson's disease is caused by the loss of dopaminergic neurons (as stated in the specification in paragraph 7 which summarizes the state of the art), not "Purkinje neurons" as recited in the claims. Accordingly, Applicants submit that claims 2, 3, 21, 34, 39, and 41-45 are novel over Rudolph *et al.* Reconsideration and withdrawal of this rejection is respectfully requested.

4.2 Claim rejections under 35 U.S.C. § 102 in view of Squadrido *et al.*

Claims 2, 3, 21, 34, 39, and 41-45 are rejected under 35 U.S.C. §102(b) as allegedly being anticipated by Squadrido *et al.* (Brit J Pharmacol 1997; 1:120:333-9). Specifically, the Examiner alleges that G-CSF was administered to rats having "vascular dysfunction and ischemic-reperfusion injury (neuron deficiency involving 'disorders of the spinal cord and vertebral column'" (page 18). Applicants cannot find the sentence in Squadrido as quoted by the Examiner. The Examiner appears to argue that these rats would inherently have a neuronal deficiency. Applicants respectfully traverse.

"It is axiomatic that for prior art to anticipate under 102 it has to meet every element of the claimed invention."[1] To prove anticipation, one must show that "each element of the claim in issue is found, either expressly or under principles of inherency, in a single prior art reference" (emphasis added).[2] "To establish inherency, the extrinsic evidence 'must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill. Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient.'"[3] "In relying upon the theory of inherency, the examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic necessarily flows from the teachings of the applied prior art."[4]

Claim 34 recites, in pertinent part, "administering an agent that mobilizes bone marrow cells to an individual having a disorder caused by a deficiency of Purkinje neurons". Squadrido *et al.* did not administer G-CSF to an organism with a deficiency of Purkinje neurons, or any other neurons for that matter. Rather, the rats of Squadrido *et al.* had vascular dysfunction and ischemic-reperfusion injury. These dysfunctions do not necessarily cause a Purkinje neuron deficiency. Furthermore, it is unclear why ischemia of the splanchnic arteries (the arteries supplying blood to

[1] *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 231 USPQ 81 (Fed. Cir. 1986).
[2] *Minnesota Mining & Manufacturing Co. v. Johnson & Johnson Orthopedics, Inc.*, 976 F.2d 1559, 24 USPQ2d 1321 (Fed. Cir. 1992).
[3] *In re Robertson*, 169 F.3d 743, 745, 49 USPQ2d 1949, 1950-51 (Fed. Cir. 1999) (citations omitted).
[4] *Ex parte Levy*, 17 USPQ2d 1461, 1464 (Bd. Pat. App. & Inter. 1990) (emphasis in original).

the viscera) would cause disorders of the spinal cord and vertebral column. Since the experimental animals of Squadrido *et al.* did not necessarily have a Purkinje neuron deficiency, claim 34 and its dependents are not inherently anticipated by Squadrido *et al.* Accordingly, Applicants submit that claims 2, 3, 21, 34, 39, and 41-45 are not anticipated by Squadrido *et al.* Reconsideration and withdrawal of this rejection is respectfully requested.

4.3 Claims rejections under 35 U.S.C. § 102 in view of McManus *et al.*

Claims 2, 3, 21, 34, 39, and 41-45 are rejected under 35 U.S.C. §102(b) as allegedly being anticipated by McManus *et al.* (Int J Radia Oncol Biol Phys 1993; 26:845-50). Specifically, the Examiner alleges that G-CSF was administered to patients having primary intracranial tumors. Although the Examiner does not elaborate why this would anticipate the claims, Applicants assume that the Examiner is again relying on the inherency theory. Applicants respectfully traverse.

A primary intracranial tumor is not a neuron deficiency. To the contrary, it results from excessive cell division. While such a tumor might (or might not) lead to increased intracranial pressure or cause neuronal death, these results will not necessarily occur. As argued above, mere probability is insufficient to prove that McManus *et al.* administered G-CSF to a patient *inherently* suffering from a Purkinje neuron deficiency. Accordingly, Applicants submit that claims 2, 3, 21, 34, 39, and 41-45 are not anticipated by McManus *et al.* Reconsideration and withdrawal of this rejection is respectfully requested.

5. Claim rejections under 35 U.S.C. §103(a)

5.1 Claim rejections under 35 U.S.C. §103(a) in view of Squadrido and Culmsee

Claims 8-13, 19, 20, and 34 are rejected under 35 U.S.C. §103(a) as allegedly unpatentable over Squadrido *et al.* in view of Culmsee *et al.* (Eur J Pharmacol 1999;379:33-45). Specifically, the Office Action asserts that Squadrido *et al.* teaches administration of G-CSF to rats having a neuronal deficiency. The Examiner then argues that Culmsee *et al.* teach administration of a neuronal factor. Applicants respectfully traverse on the following grounds.

As argued above, Squadrido *et al.* does not teach administration of G-CSF to rats having a Purkinje neuronal deficiency. Culmsee *et al.* does not remedy this deficiency. Accordingly, even assuming for the sake of argument that the cited references can be combined, the combination still fails to teach or suggest all the limitations of the claims. Therefore, reconsideration and withdrawal of this rejection on ground of 35 U.S.C. § 103(a) is respectfully requested.

5.1 Claim rejections under 35 U.S.C. §103(a) in view of Sanchez-Ramos and Bodine

Claims 2, 3, 19-21, 34, 39, and 41-45 are rejected under 35 U.S.C. §103(a) as allegedly unpatentable over Sanchez-Ramos *et al.* (WO99/56959) in view of Bodine *et al.* (Blood 1994; 84:1482-91) and Eglitis (U.S. Patent 7,022,321). Specifically, the Office Action asserts that Sanchez-Ramos teaches the transplantation of bone marrow cells into the rat brain, where the bone marrow cells allegedly take on the appearance of Purkinje neurons. The Examiner then states the Bodine supplements this teaching by establishing that G-CSF stimulates mobilization of bone marrow cells. Applicants respectfully traverse on the following grounds.

While Applicants do not, at this time, challenge the veracity of the *in vitro* cell culture data presented in the '959 Sanchez-Ramos publication, Applicants wish to draw the Examiner's attention to a publication by the inventors listed on the '959 publication. In this publication, Sanchez-Ramos *et al.* 2000 (Reference CB1 in the IDS submitted February 3, 2006) disclaim the very same *in vivo* data that is presented in Example 3 of the '959 publication.

Sanchez-Ramos *et al.* explain that beta-galactosidase is an unreliable and difficult marker to use in neurological cell transplant experiments. Neuronal cells tend to express high levels of endogenous beta-galactosidase, meaning that it is difficult to differentiate transplanted and endogenous cell types. Beginning at page 658, Sanchez-Ramos describe the beta-galactosidase approach as a "booby trap", and they describe in detail the very experiments and data that are presented in example 3 of the '959 publication. At page 660, Sanchez-Ramos et al. write, "At first blush, these results suggested the astounding result that *lacZ*-expressing, donor-derived, BMSC's had migrated extensively and had differentiated into neural cells in a site-dependent manner.

However...we were observing factitious X-gal staining that was leading to the misidentification of endogenous cells as donor-derived cells."

Therefore, the inventors of the '959 publication have themselves rejected their own data that they argued showed the *in vivo* capability of bone marrow derived cells to become neurons. Sanchez-Ramos *et al.* also refer to the discovery presented in the instant application as a result that would be "astounding". Accordingly, one of ordinary skill in the art would not read the '959 publication and the accompanying Sanchez-Ramos 2000 publication as suggesting that bone marrow derived cells can, *in vivo*, assume neuronal fates.

Furthermore, even if one skilled in the art had taken the '959 experiments at face value, that person would still not expect to see the formation of a Purkinje/bone marrow-derived heterokaryon. Claim 34 recites, in pertinent part, a "method for producing a Purkinje/bone marrow-derived heterokaryon." Nowhere does Sanchez-Ramos teach that heterokaryons were formed. Thus, there is no reason to conclude that Sanchez-Ramos was successful in producing heterokaryons. Quite the opposite; Sanchez-Ramos proposed that bone marrow-derived cells *differentiate* into Purkinje neurons. He states, "[t]hese results indicate that our treated BMSC contain pluripontent cells which differentiated into neurons." (page 25, lines 22-23). In this instance, "treated BMSC" refers to bone marrow derived cells treated *in vitro* with agents including BDNF. Sanchez-Ramos states on page 21, lines 3-4, "[p]rior to grafting, BMSC were treated for 2 days with cis-9 retinoic acid (0.5 μM) and BDNF (10 ng/ml)." Therefore, the bone-marrow cells transplanted by Sanchez-Ramos were obviously first subject to *in vitro* conditions that differ from the conditions of a bone marrow derived cell subjected to the procedure of claim 34. It is those treated cells that were later transplanted into the patient, and there is no evidence that such treated, and presumably already-differentiated (or at least committed to differentiation) cells can later form the heterokaryons recited in Claim 34. Therefore, there is no basis to conclude that Sanchez-Ramos created heterokaryons.

Accordingly, reconsideration and withdrawal of this rejection on ground of 35 U.S.C. § 103(a) is respectfully requested.

6. Conclusion

In view of the above amendments and remarks, Applicants believe the pending application is in condition for allowance.

Applicants believe no fee other than those authorized in the accompanying Amendment Transmittal is due with this response. However, if any other fee is due, please charge our Deposit Account No. 18-1945, from which the undersigned is authorized to draw under Order No. SUPP-P01-011.

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Respectfully submitted,

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